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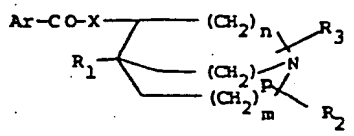
(54) **Novel compounds.**

(57) Compounds of formula (I) and pharmaceutically acceptable salts thereof:



(I)

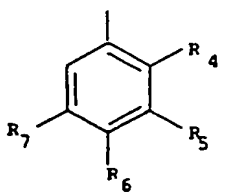
wherein:

n is 1, 2 or 3; and m and p are independently 1 or 2 such that $m + n + p \geq 4$;

X is NH; or O when Ar is of formula (a) and R_4 is hydrogen or when Ar is a group of formula (b);

R_1, R_2 and R_3 are independently hydrogen, C_{1-6} alkyl, phenyl or phenyl-C_{1-6} alkyl, which phenyl moieties may be substituted by C_{1-6} alkyl, C_{1-6} alkoxy or halogen;

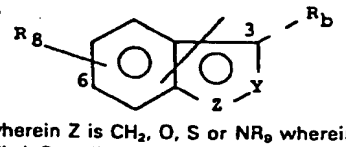
Ar is a group of formula (a):



(a)

wherein either R_4 is C_{1-6} alkoxy and one of R_5, R_6 and R_7 is hydrogen and the other two are selected from hydrogen, halogen, CF_3, C_{1-6} alkylthio, C_{1-7} acyl, C_{1-10} carboxylic acylamino, C_{1-6} alkyl S(O)n wherein n is 0, 1 or 2, nitro or amino, aminocarbonyl or aminosulphonyl optionally substituted by one or two groups selected from C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl C_{1-4} alkyl or phenyl C_{1-4} alkyl groups any of which phenyl moieties may be substituted by one or two groups selected from halogen, CF_3, C_{1-6} alkyl or C_{1-6} alkoxy; or R_4 is hydrogen and R_5, R_6 and R_7 are independently selected from hydrogen, C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio or halo; or any two on adjacent carbon atoms together are C_{1-2} alkylenedioxy and the third is hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy or halo;

or Ar is a group of formula (b):



(b)

wherein Z is CH_2, O, S or NR_9 wherein R_9 is hydrogen, C_{1-6} alkyl, C_{2-7} alkenyl, phenyl or phenyl C_{1-4} alkyl either of which phenyl moieties may be substituted by one or two of halogen, CF_3, C_{1-6} alkoxy or C_{1-6} alkyl; and Y is CH or N; or Z is CH or N and Y is NR_a or CHR_a where R_a is as defined for R_9 above;

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R_b is present when the COX linkage is attached at the phenyl ring, and is selected from hydrogen, halogen, CF_3, hydroxy, C_{1-6} alkoxy or C_{1-6} alkyl; R_1 is hydrogen, CF_3, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-7} acyl, C_{1-7} acylamino, C_{1-6} alkylsulphonylamino, N-(C_{1-6}alkylsulphonyl)-N-C_{1-4} alkylamino, C_{1-6} alkylsulphinyl, hydroxy, nitro or amino, aminocarbonyl, aminosulphonyl, aminosulphonylamino or N-(aminosulphonyl)-C_{1-4} alkylamino optionally N-substituted by
one or two groups selected from C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl C_{1-4} alkyl, phenyl or phenyl C_{1-4} alkyl groups or optionally N-disubstituted by C_{4-5} polymethylene; having gastric motility enchancing activity and/or anti-emetic activity and/or 5-HT antagonist activity, a process for their preparation and their use as pharmaceuticals.

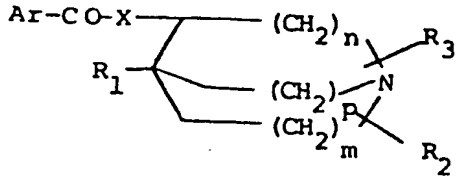
NOVEL COMPOUNDS

This invention relates to substituted benzamides and benzoates having pharmacological activity, to a process for their preparation and to their use as pharmaceuticals.

EP-A-99789 discloses a group of benzamides having a 3-quinuclidinyl side chain and having gastric motility enhancing activity. GB 2125398A discloses a group of benzamides and benzoates having a quinuclidinyl side chain and having serotonin M antagonist activity.

A structurally distinct group of compounds has now been discovered which compounds have gastric motility enhancing activity and/or anti-emetic activity and/or 5-HT receptor antagonist activity.

Accordingly, the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

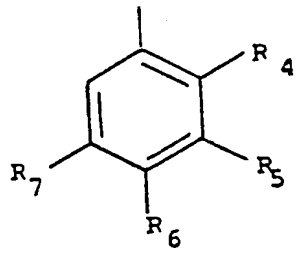
wherein:

n is 1, 2 or 3; and m and p are independently 1 or 2 such that $m + n + p \geq 4$;

X is NH; or O when Ar is of formula (a) and R_4 is hydrogen or when Ar is a group of formula (b);

R_1, R_2 and R_3 are independently hydrogen, C_{1-6} alkyl, phenyl or phenyl-C_{1-6} alkyl, which phenyl moieties may be substituted by C_{1-6} alkyl, C_{1-6} alkoxy or halogen;

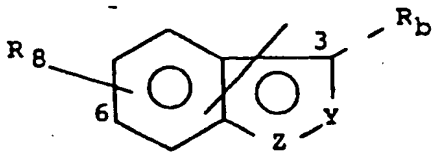
Ar is a group of formula (a):



(a)

wherein either R_4 is C_{1-6} alkoxy and one of R_5, R_6 and R_7 is hydrogen and the other two are selected from hydrogen, halogen, CF_3, C_{1-6} alkylthio, C_{1-7} acyl, C_{1-10} carboxylic acylamino, C_{1-6} alkyl S(O)n wherein n is 0, 1 or 2, nitro or amino, aminocarbonyl or aminosulphonyl optionally substituted by one or two groups selected from C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl C_{1-4} alkyl or phenyl C_{1-4} alkyl groups any of which phenyl moieties may be substituted by one or two groups selected from halogen, CF_3, C_{1-6} alkyl or C_{1-6} alkoxy; or R_4 is hydrogen and R_5, R_6 and R_7 are independently selected from hydrogen, C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio or halo; or any two on adjacent carbon atoms together are C_{1-2} alkylenedioxy and the third is hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy or halo;

or Ar is a group of formula (b):



(b)

wherein Z is CH_2, O, S or NR_9 wherein R_9 is hydrogen, C_{1-6} alkyl, C_{2-7} alkenyl, phenyl or phenyl C_{1-4} alkyl either of which phenyl moieties may be substituted by one or two of halogen, CF_3, C_{1-6} alkoxy or C_{1-6} alkyl; and Y is CH or N; or Z is CH or N and Y is NR_a or CHR_a where R_a is as defined for R_9 above;

R_b is present when the COX linkage is attached at the phenyl ring, and is selected from hydrogen, halogen, CF_3, hydroxy, C_{1-6} alkoxy or C_{1-6} alkyl; R_1 is hydrogen, CF_3, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-7} acyl, C_{1-7} acylamino, C_{1-6} alkylsulphonylamino, N-(C_{1-6} alkylsulphonyl)-N-C_{1-4} alkylamino, C_{1-6} alkylsulphinyl, hydroxy, nitro or amino, aminocarbonyl, aminosulphonyl, aminosulphonylamino or N-(aminosulphonyl)-C_{1-4} alkylamino optionally N-substituted by one or two groups selected from C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl C_{1-4} alkyl, phenyl or phenyl C_{1-4} alkyl groups or optionally N-disubstituted by C_{4-5} polymethylene.

Suitable values for n include 1, 2 or 3, often 2. Preferably n is 2 and m and p are both 1.

X is often NH.

Suitable examples of R_1, R_2, and R_3 include hydrogen, methyl, ethyl, n- and iso-propyl, n-, iso-, sec- and tert-
butyl; phenyl, phenylmethyl and phenylethyl, which phenyl moieties may be substituted by one or two methyl, ethyl, n- and iso-propyl, n-, iso-, sec- and tert-butyl; methoxy, ethoxy and n- and iso-propoxy; CF_3, fluoro, chloro or bromo.

Often R_1, R_2 and R_3 are hydrogen or methyl, preferably they are all hydrogen.

When Ar is a group of formula (a), examples of R_4 when C_{1-6} alkoxy include methoxy, ethoxy and n- and iso-propoxy. Preferably R_4 is a methoxy group.

Suitable examples of R_6 and R_7 then include the following atoms and groups: hydrogen; chloro, bromo, CF_3, methylthio, ethylthio, n and iso-propylthio; formyl, acetyl, propionyl, n- and iso-butyryl; formylamino, acetylamino, propionylamino, n- and iso-butyrylamino; methyl, ethyl and n- and iso-propylsulphone, -sulphinyl, -thia; nitro; methoxy, ethoxy and n- and iso-propoxy; hydroxy; amino, aminosulphonyl substituted by one or two methyl, ethyl, n- or iso-propyl groups, or by C_2, C_4 or C_5 cycloalkyl or by benzyl optionally subtstituted as defined above. Particularly suitable R_6 and R_7 groups include hydrogen, halogen, and amino; and as ''intermediates'', acylamino and nitro, which can conveniently be converted to the corresponding amino groups.

Particularly preferred R_6 groups include 4-amino and 4-acylamino. Most preferably R_6 is 4-amino. Particularly preferred R_7 groups include 5-halo, such as 5-chloro.

In another group of compounds R_6 is hydrogen, 4-halo (eg chloro), or amino; and R_7 is 5-C_{1-6} alkyl S $(O)_n$ (such as 5-methylsulphonyl, -sulphinyl or -thia) or 5-optionally alkylated aminosulphonyl.

When R_4 is hydrogen, examples of R_5 include halo, such as chloro and C_{1-6} alkoxy, such as methoxy. Preferably R_5 is chloro.

Examples of R_6 then include hydrogen, halo, such as chloro, hydroxy and C_{1-6} alkoxy such as methoxy. Preferably R_6 is hydrogen or chloro.

Examples or R_7 then include hydrogen, halo such as chloro and C_{1-6} alkoxy, such as methoxy. Preferably R_7 is hydrogen or chloro.

Z is often NR_9 and Y is CH or N; or Z is N and R_a is as defined for R_9.

Suitable values for R_9 or R_a include hydrogen, methyl, ethyl, n- and iso-propyl; vinyl, prop-1-enyl, prop-2-enyl, 1-methylvinyl, but-1-enyl, but-2-enyl, but-3-enyl, 1-methylenepropyl, 1-methylprop-1-enyl and 1-methylprop-2-yl in their E and Z forms where stereoisomerism exists, phenyl and benzyl optionally substituted by one or two of chloro, bromo, CF_3, methoxy, ethoxy, n- and iso-propoxy, methyl, ethyl, n- and iso-propyl. Often R_9/R_a is hydrogen, methyl or ethyl.

Suitable values for R_b when present include hydrogen, chloro, bromo, CF_3, methoxy, ethoxy, n- and iso-propoxy, methyl, ethyl, n- and iso-propyl.

Often the -COX- linkage is attached at positions 3 or 6, as depicted in formula (b).

The pharmaceutically acceptable salts of the compounds of the formula (I) include acid addition salts with conventional acids such as hydrochloric, hydrobromic, boric, phosphoric, sulphuric acids and pharmaceutically acceptable organic acids such as acetic, tartaric, maleic, citric, succinic, benzoic, ascorbic, methanesulphonic, α-keto glutaric, α-glycerophosphoric, and glucose-1-phosphoric acids.

The pharmaceutically acceptable salts of the compounds of the formula (I) are usually acid addition salts with acids such as hydrochloric, hydrobromic, phosphoric, sulphuric, citric, tartaric, lactic and acetic acid.

Preferably the acid addition salt is the hydrochloride salt.

Examples of pharmaceutically acceptable salts include quaternary derivatives of the compounds of formula (I) quaternised by compounds such as R_{10}-T wherein R_{10} is C_{1-6} alkyl, phenyl-C_{1-6} alkyl or C_{5-7} cycloalkyl, and T is a radical corresponding to an anion of an acid. Suitable examples of R_{10} include methyl, ethyl and n- and iso-propyl; and benzyl and phenethyl. Suitable examples of T include halide such as chloride, bromide and iodide.

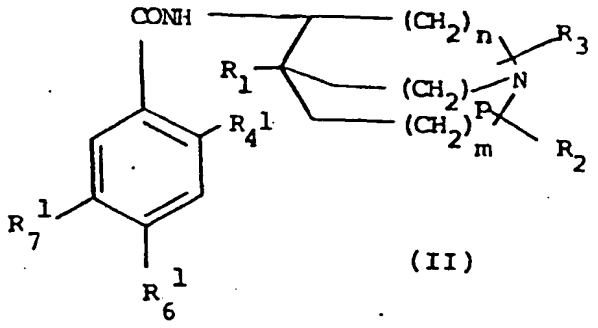
Examples of pharmaceutically acceptable salts of the compounds of formula (I) also include internal salts such as pharmaceutically acceptable N-oxides.

The compounds of the formula (I), their pharmaceutically acceptable salts, (including quaternary derivatives and N-oxides) may also form pharmaceutically acceptable solvates, such as hydrates, and these are included whenever a compound of formula (I) or a salt thereof is herein referred to..

It will of course be realised that some of the compounds of the formula (I) have chiral or prochiral centres and thus are capable of existing in a number of stereoisomeric forms including enantiomers. The invention extends to each of these stereoisomeric forms (including enantiomers), and to mixtures thereof (including racemates). The different stereoisomeric forms may be separated one from the other by the usual methods.

It will also be realised that compounds of the formula (I) wherein R_9 is hydrogen can exist as two tautomeric forms i.e. that wherein R_9 is hydrogen and Y is CH or N and that wherein Ra is hydrogen and Z is N. The invention extends to each of these forms and to mixtures thereof. The predominant tautomeric form is usually that wherein R_9 is hydrogen.

A group of compounds within formula (I) is of formula (II):

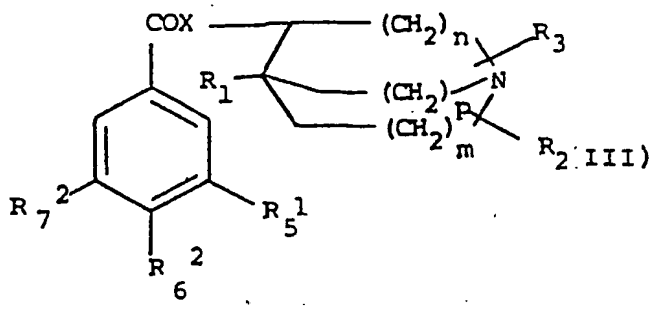


(II)

wherein R_4^1 is C_{1-6} alkoxy;
R_6^1 is amino or C_{1-7} alkanoylamino;
R_7^1 is halo or C_{1-6} alkylthio;

and the remaining variables are as defined in formula (I). Suitable examples and preferred values for the variables are as described for the corresponding variables under formula (I).

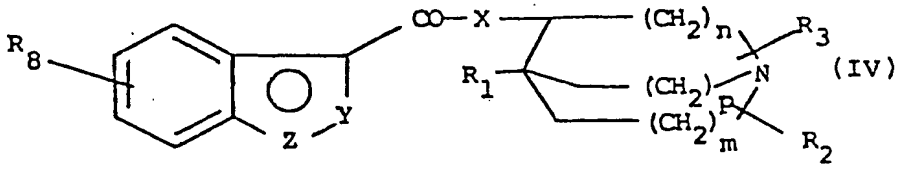
There is a further group of compounds within formula (I) of formula (III):



wherein R_5^1 is halo, C_{1-6} alkoxy or C_{1-6} alkyl;
R_6^2 is hydrogen or C_{1-6} alkoxy;
R_7^2 is halo, C_{1-6} alkoxy or C_{1-6} alkyl; and the remaining variables are as defined in formula (I).

Suitable examples and preferred values for the variables are as described for the corresponding variables under formula (I).

There is another group of compounds within formula (I) of formula (IV):



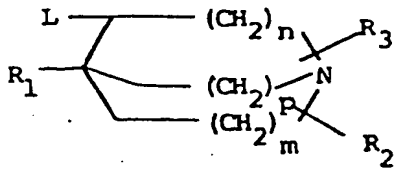
wherein the variables are as defined in formula (I).

Suitable examples and preferred values for the varibles are as described for the corresponding variables under formula (I).

The invention also provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises reacting a compound of formula (V):

(V)

with a compound of formula (VI):



(VI)

wherein

G is COQ where Q is a leaving group; and L is NH_2 or OH or a reactive derivative thereof and the remaining variables are as hereinbefore defined; and thereafter optionally converting any R_4, R_5, R_6, R_7, R_8, R_a and R_b group to another R_4, R_5, R_6, R_7, R_8, R_a and R_b group respectively, and optionally forming a pharmaceutically acceptable salt of the resultant compound of formula (I).

Examples of leaving groups Q, displaceable by a nucleophile, include halogen such as chloro and bromo, hydroxy, carboxylic acyloxy such as C_{1-4} alkanoyloxy or

C_{1-4} alkoxycarbonyloxy and activated hydrocarbyloxy such as pentachlorophenoxy.

Alternatively, when G is COQ, Ar is of formula (b) and Z is NH in formula (V), a nitrogen heterocycle may act as the leaving group i.e. that obtained by reaction of a compound of formula (V) wherein G is CO_2H and Z is NH with thionyl chloride to give a diindazolo[2,3-a,2',3'-d]pyrazine-7,14-dione.

If a group Q is a halide, then the reaction is preferably carried out at non-extreme temperatures in an inert non-hydroxylic solvent, such as benzene, dichloromethane, toluene, diethyl ether, THF (tetrahydrofuran) or DMF (dimethylformamide). It is also preferably carried out in the presence of an acid acceptor, such as an organic base, in particular a tertiary amine, such as triethylamine, trimethylamine, pyridine or picoline, some of which can also function as the solvent. Alternatively, the acid acceptor can be inorganic, such as calcium carbonate, sodium carbonate or potassium carbonate. Temperatures of 0^{o}-$100^{o}C$, in particular 10-$80^{o}C$ are suitable.

If a group Q is hydroxy, then the reaction is generally carried out in an inert non-hydroxylic solvent, such as dichloromethane, THF or DMF optionally in the presence of a dehydrating catalyst, such as a carbodiimide, for example dicyclohexylcarbodiimide. The reaction may be carried out at any non-extreme temperature, such as -10 to $100^{o}C$, for example, 0 to $80^{o}C$. Generally, higher reaction temperatures are employed with less active compounds whereas lower temperatures are employed with the more active compounds.

If a group Q is carboxylic acyloxy, then the reaction is preferably carried in substantially the same manner as the reaction when Q is halide. Suitable examples of acyloxy leaving groups include C_{1-4} alkanoyloxy and C_{1-4} alkoxycarbonyloxy, in which case the reaction is preferably carried out in an inert solvent, such as dichloromethane, at a non-extreme temperature for example ambient temperatures in the presence of an acid acceptor, such as triethylamine. C_{1-4} alkoxycarbonyloxy leaving groups may be generated in situ by treatment of the corresponding compound wherein Q is hydroxy with a C_{1-4} alkyl chloroformate.

If a group Q is activated hydrocarbyloxy then the reaction is preferably carried out in an inert polar solvent, such as dimethylformamide. It is also preferred that the activated hydrocarbyloxy group is a pentachlorophenyl ester and that the reaction is carried out at ambient temperature.

When the leaving group Q is a nitrogen heterocycle as hereinbefore described the reaction is carried out in a similar manner as when Q is a halide.

When L is OH or a reactive derivative thereof, the reactive derivative is often a salt, such as the sodium or lithium salt.

Pharmaceutically acceptable salts of the compounds of this invention may be formed conventionally.

The salts may be formed for example by reaction of the base compound of formula (I) with a pharmaceutically acceptable organic or inorganic acid.

It will be apparent that compounds of the formula (I) containing an R_4, R_5, R_6, R_7, R_8, R_a or R_b group which is convertible to another R_4, R_5, R_6, R_7, R_8, R_a or R_b group are useful novel intermediates. A number of such conversions is possible not only for the end compounds of formula (I), but also for their intermediates as follows:

(i) a hydrogen substituent is convertible to a nitro substituent by nitration;

(ii) a nitro substituent is convertible to an amino substituent by reduction;

(iii) a C_{1-7} acylamino substituent is convertible to an amino substituent by deacylation;

(iv) an amino substituent is convertible to a C_{1-4} acylamino substituent by acylation with a carboxylic acid derivative;

(v) a hydrogen substituent is convertible to a halogen substituent by halogenation;

(vi) a C_{1-6} alkylthio or C_{1-6} alkylsulphinyl substituent is convertible to a C_{1-6} alkylsulphinyl or a C_{1-6} alkylsulphonyl substituent respectively by oxidation;

(vii) an amino, aminocarbonyl, aminosulphonyl, aminosulphonylamino or N-(aminosulphonyl)-N-C_{1-4} alkylamino substituent is convertible to a corresponding substituent substituted by one or two groups selected from C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{1-4} alkyl or phenyl C_{1-4} alkyl groups any of which phenyl groups may be

substituted by one or more groups selected from halogen, trifluoromethyl, C_{1-6} alkyl, C_{1-6} alkoxy and nitro, or disubstituted by C_{4-5} polymethylene , by N-alkylation;

(viii) an amino substituent is convertible to a C_{1-6} alkylsulphonylamino group or an aminosulphonylamino group optionally N-substituted as defined by acylation with a C_{1-6} alkylsulphonic acid or di-substituted amisosulphonyl chloride.

(ix) A C_{1-4} alkylamino substituent group is convertible to a N-(C_{1-6} alkylsulphonyl)N-C_{1-4} alkylamino group or an N-(amino sulphonyl)N-C_{1-4} alkylamino group optionally N-substituted as defined by acylation with a C_{1-6} alkylsulphonic acid or di-substituted amisosulphonyl chloride.

Conversions (i) to (ix) are only exemplary and are not exhaustive of the possibilities.

In regard to (i), nitration is carried out in accordance with known procedures.

In regard to (ii), the reduction is carried out with a reagent suitable for reducing nitroanisole to aminoanisole.

In regard to (iii), deacylation is carried out by treatment with a base, such as an alkali metal hydroxide.

In regard to (iv), (viii), and (ix) the acylation is carried out with an acylating agent, such as the corresponding acid or acid chloride. Formylation is carried out with the free acid.

In regard to (v), halogenation is carried out with conventional halogenating agents.

In regard to (vi), oxidation is carried out at below ambient temperatures in a non-aqueous solvent, such as a chlorinated hydrocarbon, in the presence of an organic peracid, such as 3-chloroperbenzoic acid, or in water in the presence of a soluble strong inorganic oxidant, such as an alkali metal permanganate or in aqueous hydrogen peroxide. It will be realised that this process may also N-oxidise the $N\lesssim$ moiety and suitable precautions will routinely be taken by the skilled man.

In regard to (vii), alkylation is carried out with a corresponding alkylating agent such as the chloride or bromide under conventional conditions.

Before carrying out any of these conversions, the effect, if any, on other substituents should be considered, and such reagents as are appropriate should be selected together with the adoption of such precautionary measures as are necessary. For example, O-alkylation and O-acylation may also produce N-alkylated and N-acylated products respectively unless the nitrogen atom(s) is (are) previously protected. This may be conveniently achieved by carrying out the alkylation or acylation reaction in a strong acid, such as trifluoroacetic acid, which protonates, and thereby protects, the nitrogen atom(s).

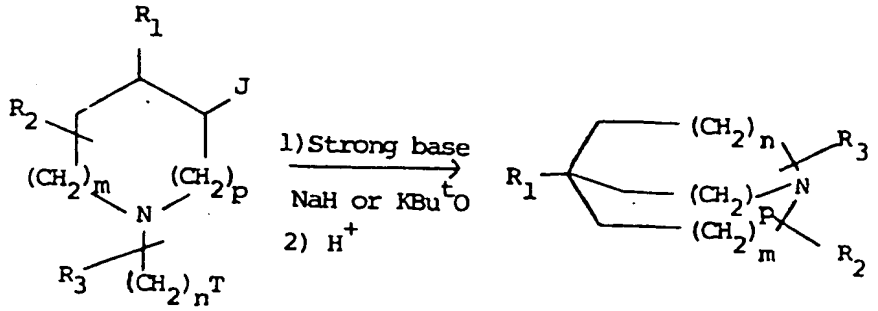
The compounds of formula (V) are known or are preparable analogously to, or routinely from, known compounds.

Compounds of formula (VI) are novel and form an aspect of the present invention. They may be prepared from the corresponding ketones in accordance with the processes described in the descriptions hereinafter or by analogous methods thereto.

Compounds of formula (VI) wherein L is NH_2 may be prepared from the corresponding ketone by reaction with hydroxylamine to form the oxime which then may be reduced conventionally using AlH_3 or sodium/amyl alcohol.

Compounds of formula (VI) wherein L is OH may be prepared by reduction of the corresponding ketone by conventional methods such as lithium aluminium hydride reduction.

The ketones (of formula (VII)) may be prepared by methods analogous to those known in the art such as Dieckmann or Thorpe cyclisation or ring expansion methods as follows:



(VIII) (VII)

wherein J and T in formula (VIII) are independently cyano groups or C_{1-4} alkyl ester groups.

The compounds of the present invention have gastric motility enhancing activity and/or anti-emetic activity and/or 5-HT antagonist activity. Compounds having gastric motility enhancing activity are useful in the treatment of disorders such as retarded gastric emptying, dyspepsia, flatulence, oesophagal reflux and peptic ulcer. Compounds having 5-HT antagonist activity are useful in the treatment of migraine, cluster headaches, trigeminal neuralgia and/or cytotoxic agent or radiation induced nausea and vomiting. Examples of cytotoxic agents include cisplatin, doxorubicin and cyclophosphamide. Compounds which are 5-HT antagonists may also be of potential use in the treatment of CNS disorders such as anxiety and psychosis; arrhythmia, obesity and irritable bowel syndrome.

The compounds of formula (I) of particular interest for their 5-HT antagonist activity are the compounds of formula (I) wherein Ar is of formula (a) and R_4 is hydrogen, or Ar is of formula (b). The compounds of formula (I) of particular interest for their gastric motility enhancing activity and anti-emetic activity are the compounds of formula (I) where Ar is of formula (a) and R_4 is C_{1-6} alkoxy.

The invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

Such compositions are prepared by admixture and are suitably adapted for oral or parenteral administration,

and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable and infusable solutions or suspensions or suppositories. Orally administrable compositions are preferred, since they are more convenient for general use.

Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers, diluents, tabletting agents, lubricants, disintegrants, colourants, flavourings, and wetting agents. The tablets may be coated according to well known methods in the art, for example with an enteric coating.

Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpolypyrrolidone and starch derivatives such as sodium starch glycollate. Suitable lubricants include, for example, magnesium stearate.

Suitable pharmaceutically acceptable wetting agents include sodium lauryl sulphate. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil,

fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

Oral liquid preparations are usually in the form of aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs or are presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and flavouring or colouring agents.

The oral compositions may be prepared by conventional methods of blending, filling or tabletting. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art.

For parenteral administration, fluid unit dose forms are prepared containing a compound of the present invention and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing.

Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilised by exposure of ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound of the invention.

The invention further provides a method of treatment or prophylaxis of disorders relating to impaired gastro-intestinal motility and/or emesis and/or migraine, cluster headaches, trigeminal neuralgia and/or cytotoxic agent or radiation induced vomiting in mammals, such as humans, which comprises the administration of an effective amount of a compound of the formula (I) or a pharmaceutically acceptable salt thereof.

An amount effective to treat the disorders herein-before described depends on the relative efficacies of the compounds of the invention, the nature and severity of the disorder being treated and the weight of the mammal. However, a unit dose for a 70kg adult will normally contain 0.5 to 1000mg for example 1 to 500mg, of the compound of the invention. Unit doses may be administered once or more than once a day, for example, 2, 3 or 4 times a day, more usually 1 to 3 times a day, that is in the range of approximately 0.001 to 50 mg/kg/day, more usually 0.002 to 25 mg/kg/day.

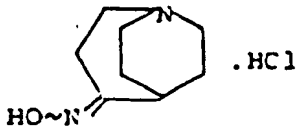
No adverse toxicological effects are indicated at any of the aforementioned dosage ranges.

The invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use as an active therapeutic substance, in particular for use in the treatment of disorders relating to impaired gastro-intestinal motility and/or emesis and/or migraine, cluster headaches, trigeminal neuralgia and/or cytotoxic agent or radiation induced vomiting.

The following Examples illustrate the preparation of compounds of formula (I); the following Descriptions illustrate the preparation of intermediates.

Description 1

1-Azabicyclo[3.2.2.]nonan-4-one oxime hydrochloride (D1)



(D1)

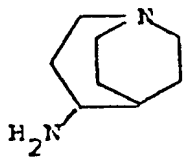
Hydroxylamine hydrochloride (2.1g) was added to a solution of 1-azabicyclo[3.2.2.]nonan-4-one (2.77g) in ethanol (30ml) and the mixture was heated under reflux for 2h. On cooling the reaction mixture to room temperature, the white solid was collected by filtration and dried in vacuo to give the title compound (2.84g, 75%).

^{1}H-NMR (DMSO-d_6)

δ	11.65	(brs. 1H)
	10.75,10.65	(2s, 1H)
	3.70-2.40	(m, 9H)
	2.35-1.50	(m, 4H)

Description 2

4-Amino-1-azabicyclo[3.2.2]nonane (D2)

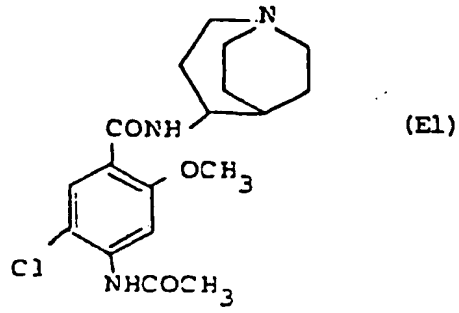


(D2)

Sodium (5.6g) was added portionwise to a suspension of 1-azabicyclo[3.2.2]nonan-4-one oxime hydrochloride (D1) (2.8g) in amyl alcohol (100ml) which was heated under reflux. After all the sodium had reacted, the mixture was cooled to 50° and water (20ml) was added carefully. The aqueous phase was separated and the amyl alcohol was extracted with 5N hydrochloric acid (2 x 15ml). The combined acid extract was washed with diethyl ether and the solvent evaporated in vacuo to give 4-amino-1-azabicyclo[3.2.2]nonane hydrochloride. The hydrochloride salt was basified with 40% sodium hydroxide and the aqueous phase was saturated with potassium carbonate, extracted with diethyl ether, dried (Na_2SO_4) and the solvent evaporated in vacuo to give the title compound (1.4g, 68%).

Example 1

(±) 4-Acetamido-5-chloro-2-methoxy-N-[4'-(1'-azabicyclo[3.2.2]nonyl)]benzamide (E1)



(E1)

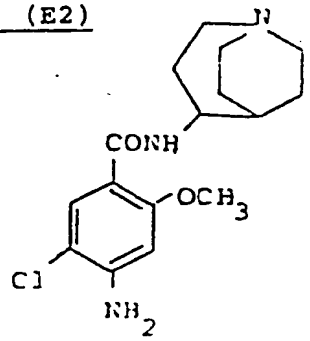
To 4-acetamido-5-chloro-2-methoxybenzoyl chloride (1.96g) in dry dichloromethane (75ml) and triethylamine (0.89ml) at 0° was added the crude 4-amino-1-azabicyclo[3.2.2]nonane (D2) (0.9g) in dry dichloromethane (20ml). The reaction mixture was stirred at room temperature for 2h, then treated with 2.5N sodium hydroxide solution (10ml). The organic phase was separated, dried (Na_2SO_4) and the solvent evaporated in vacuo to give the title compound (E1) (2.15g, 92%) as a white foam.

^{1}H-NMR ($CDCl_3$)

δ	8.25	(s, 1H)
	8.15	(s, 1H)
	7.85	(m, 2H)
	4.45-3.80	(m, 1H)
	3.90	(s, 3H)
	3.40-2.40	(m, 6H)
	2.40-1.10	(m, 7H)
	2.25	(s, 3H)

Example 2

(±) 4-Amino-5-chloro-2-methoxy-N-[4'-(1'-azabicylo [3.2.2]nonyl)]benzamide (E2)



(E2)

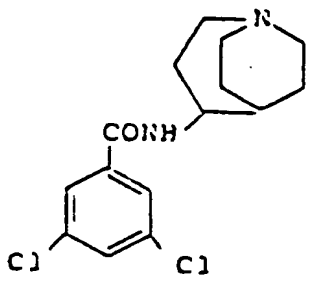
(±) 4-Acetamido-5-chloro-2-methoxy-N-[4'-(1'-azabicyclo [3.2.2]nonyl)]benzamide (2.15g) was heated under reflux in ethanol (40ml) and 2.5N sodium hydroxide solution (4.7ml) for 2h. After concentration in vacuo, the aqueous residue was extracted with dichloromethane (2 x 100ml). The organic phase was dried (Na_2SO_4), concentrated and the residue purified by column chromatography on alumina, eluting with $CHCl_3$ to give the title compound (E2) (0.58g, 31%) m.p. 168-72°.

^{1}H-NMR ($CDCl_3$)

δ	8.10 (s, 1H)
	7.90-7.65 (m, 1H)
	6.30 (s, 1H)
	4.65-3.70 (m, 3H)
	3.90 (s, 3H)
	3.40-2.60 (m, 6H)
	2.30-1.30 (m, 7H)

Example 3

(±) 3,5-Dichloro-N-[4'-(1'-azabicyclo[3.2.2]nonyl)] benzamide (E3)



(E3)

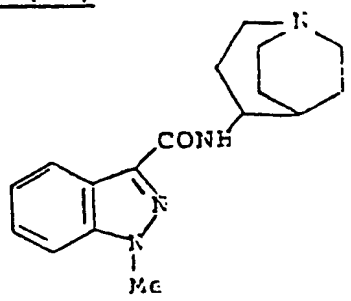
Following the procedure outlined in Example 1, reaction of 4-amino-1-azabicyclo[3.2.2]nonane (D2) (0.25g) with 3,5-dichlorobenzoyl chloride (0.45g) afforded (±) 3,5-dichloro-N-[4'-(1'-azabicyclo[3.2.2]nonyl)] benzamide (E3) (0.35g, 63%) m.p. 169-70°

^{1}H-NMR ($CDCl_3$)

δ	7.60 (d, 2H)
	7.48 (m, 1H)
	6.25 (bd, 1H)
	4.21 (quin, 1H)
	3.34-3.20 (m, 1H)
	3.18-2.77 (m, 5H)
	2.18-1.54 (m, 7H)

Example 4

(±) 1-Methylindazol-3-yl-N-[4'-(1'-azabicyclo[3.2.2]nonyl)]carboxamide (E4)



(E4)

Following the procedure outlined in Example 1, reaction of 4-amino-1-azabicyclo[3.2.2]nonane (D2) (0.1g) with 1-methyl-3-indazoloyl chloride (0.17g) afforded (±) 1-methylindazol-3-yl-N-(4'-(1'-azabicyclo[3.2.2]nonyl)] carboxamide (E4) (0.065g, 31%) m.p. 117-8°

^{1}H-NMR ($CDCl_3$)

δ	8.35	(m, 1H)
	7.50-7.25	(m, 3H)
	7.05	(bd, 1H)
	4.39-4.27	(m, 1H)
	4.10	(s, 3H)
	3.40-2.84	(m, 6H)
	2.31-1.57	(m, 7H)

Pharmacology

Antagonism of the von Bezold-Jarisch reflex

The compounds were evaluated for antagonism of the von Bezold-Jarisch reflex evoked by 5-HT in the anaesthetised rat according to the following method:

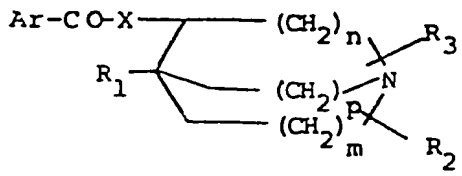
Male rats 250-350g, were anaesthetised with urethane (1.25g/kg intraperitoneally) and blood pressure and heart rate recorded as described by Fozard J.R. et al., J. Cardiovasc. Pharmacol. 2, 229-245 (1980). A submaximal dose of 5-HT (usually 6µg/kg) was given repeatedly by the intravenous route and changes in heart rate quantified. Compounds were given intravenously and the concentration required to reduce the 5-HT-evoked response to 50% of the control response (ED_{50}) was then determined.

The compound of Example 3 had an ED_{50} of 0.008 mg/kg i.v.

C

Claims

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

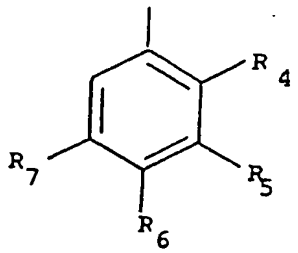
wherein:

n is 1, 2 or 3; and m and p are independently 1 or 2 such that $m + n + p \geq 4$;

X is NH; or O when Ar is of formula (a) and R_4 is hydrogen or when Ar is a group of formula (b);

R_1, R_2 and R_3 are independently hydrogen, C_{1-6} alkyl, phenyl or phenyl-C_{1-6} alkyl, which phenyl moieties may be substituted by C_{1-6} alkyl, C_{1-6} alkoxy or halogen;

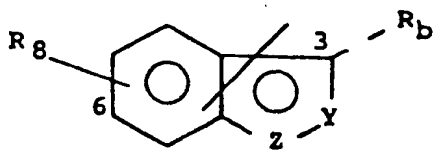
Ar is a group of formula (a):



(a)

wherein either R_4 is C_{1-6} alkoxy and one of R_5, R_6 and R_7 is hydrogen and the other two are selected from hydrogen, halogen, CF_3, C_{1-6} alkylthio, C_{1-7} acyl, C_{1-10} carboxylic acylamino, C_{1-6} alkyl S(O)n wherein n is 0, 1 or 2, nitro or amino, aminocarbonyl or aminosulphonyl optionally substituted by one or two groups selected from C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl C_{1-4} alkyl or phenyl C_{1-4} alkyl groups any of which phenyl moieties may be substituted by one or two groups selected from halogen, CF_3, C_{1-6} alkyl or C_{1-6} alkoxy; or R_4 is hydrogen and R_5, R_6 and R_7 are independently selected from hydrogen, C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio or halo; or any two on adjacent carbon atoms together are C_{1-2} alkylenedioxy and the third is hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy or halo;

or Ar is a group of formula (b):



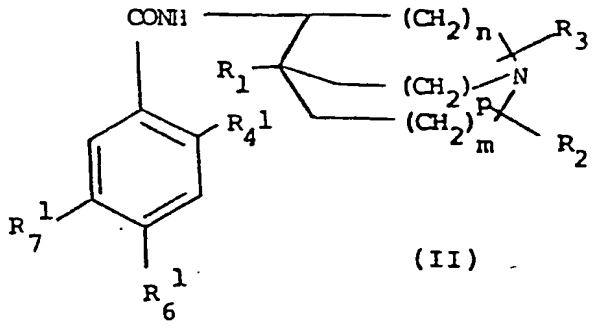
(b)

wherein Z is CH_2, O, S or NR_9 wherein R_9 is hydrogen, C_{1-6} alkyl, C_{2-7} alkenyl, phenyl or phenyl C_{1-4} alkyl either of which phenyl moieties may be substituted by one or two of halogen, CF_3, C_{1-6} alkoxy or C_{1-6} alkyl; and Y is CH or N; or Z is CH or N and Y is NR_a or CHR_a where R_a is as defined for R_9 above;

R_b is present when the COX linkage is attached at the phenyl ring, and is selected from hydrogen, halogen, CF_3, hydroxy, C_{1-6} alkoxy or C_{1-6} alkyl; R_1 is

hydrogen, CF_3, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-7} acyl, C_{1-7} acylamino, C_{1-6} alkylsulphonylamino, N-(C_{1-6} alkylsulphonyl)-N-C_{1-4} alkylamino, C_{1-6} alkylsulphinyl, hydroxy, nitro or amino, aminocarbonyl, aminosulphonyl, aminosulphonylamino or N-(aminosulphonyl)-C_{1-4} alkylamino optionally N-substituted by one or two groups selected from C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl C_{1-4} alkyl, phenyl or phenyl C_{1-4} alkyl groups or optionally N-disubstituted by C_{4-5} polymethylene.

2. A compound according to claim 1 of formula (II):

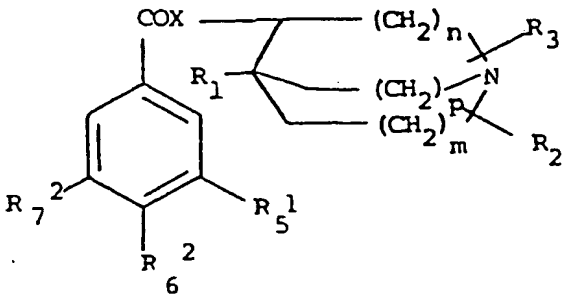


(II)

wherein R_4^1 is C_{1-6} alkoxy;
R_6^1 is amino or C_{1-7} alkanoylamino;
R_7^1 is halo or C_{1-6} alkylthio; and the remaining variables are as defined in claim 1.

3. A compound according to claim 2 wherein R_4^1 is methoxy, R_6^1 is amino and R_7^1 is chloro or bromo.

4. A compound according to claim 1 of formula (III):

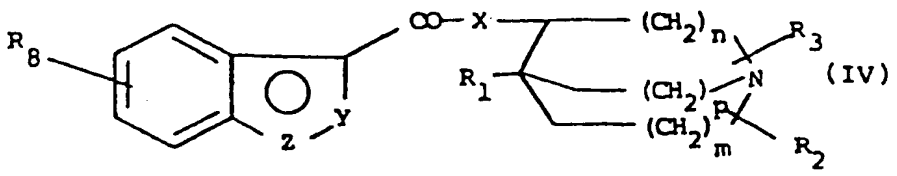


(III)

wherein R_5^1 is halo, C_{1-6} alkoxy or C_{1-6} alkyl;
R_6^2 is hydrogen or C_{1-6} alkoxy;
R_7^2 is halo, C_{1-6} alkoxy or C_{1-6} alkyl; and the remaining variables are as defined in claim 1.

5. A compound according to claim 3 wherein R_5^1 and R_7^2 are both chloro or both methyl and R_6^2 is hydrogen.

6. A compound according to claim 1 of formula (IV):



(IV)

wherein the variables are as defined is claim 1.

7. A compound according to claim 6 wherein Y is N and Z is NR_9 as defined in claim 1.

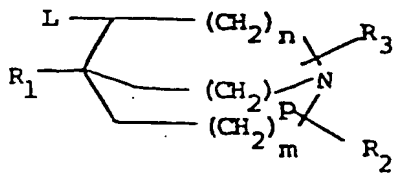
8. A compound according to any one of claims 1 to 7 wherein R_1, R_2 and R_3 are all hydrogen, m is 1, n is 2 and p is 1.

9. 4-Amino-5-chloro-2-methoxy-N-[4'-(1'-azabicylo [3.2.2]nonyl)]benzamide,
3,5-dichloro-N-[4'-(1'-azabicyclo[3.2.2]nonyl)] benzamide,
1-methylindazol-3-yl-N-[4'-(1'-azabicyclo[3.2.2] nonyl)]carboxamide,
or a pharmaceutically acceptable salt of any of the foregoing.

10. A process for the preparation of a compound of formula (I) as defined in claim 1, or a pharmaceutically acceptable salt thereof, which process comprises reacting a compound of formula (V):

Ar G (V)

with a compound of formula (VI):



(VI)

wherein

G is COQ where Q is a leaving group; and L is NH_2 or OH or a reactive derivative thereof and the remaining variables are as hereinbefore defined; and thereafter optionally converting any R_4, R_5, R_6, R_7, R_8, R_a and R_b group to another R_4, R_5, R_6, R_7, R_8, R_a and R_b group respectively, and optionally forming a pharmaceutically acceptable salt of the resultant compound of formula (I).

11. A compound of formula (VI) as defined in claim 10.

12. 4-Amino-1-azabicyclo[3.2.2]nonane.

13. A pharmaceutical composition comprising a compound according to any one of claims 1 to 9, and a pharmaceutically acceptable carrier.

14. A compound according to any one of claims 1 to 9 for use in the treatment of disorders relating to impaired gastro-intestinal motility and/or emesis and/or migraine, cluster headaches, trigeminal neuralgia and/or cytotoxic agent or radiation induced nausea and vomiting.

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

021477;
Application number

EP 86306221.2

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. ⁴)
X	CHEMICAL ABSTRACTS, vol. 74, no. 15, April 12, 1971, Columbus, Ohio, USA V.YA. VOROB'EVA "Synthesis of 4-oxo-1-azabicyclo[3.2.2.]nonane" page 433, column 1, abstract no. 76304a & Khim. Geterosikl. Soedin. 1970, (8), 1037-40 --	11	C 07 D 471/08 C 07 D 487/08 A 61 K 31/55
X	CHEMICAL ABSTRACTS, vol. 62, no. 11, May 24, 1965, Columbus, Ohio, USA K.A. ZAITSEVA "Effects of some tertiary and quaternary quinuclidine derivatives and the like on cholinoreactive systems" column 13 727, abstract no. 13727f & Farmacol. i Toksikol. 27(6), 686-90 (1964) --	11	
A		1	C 07 D 471/00 C 07 D 487/00 C 07 D 453/00

TECHNICAL FIELDS SEARCHED (Int. Cl. ⁴)

INCOMPLETE SEARCH

The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims.

Claims searched completely: 1-13
Claims searched incompletely: -
Claims not searched: 14
Reason for the limitation of the search:

(Article 52(4) EPC; method for treatment of human or animal body by therapy)

Place of search	Date of completion of the search	Examiner
VIENNA	18-11-1986	ONDER

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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0214772
Application number

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

EP 86306221.2

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
A	WO - A1 - 85/02 847 (SANDOZ) * Claim 1; page 28, lines 23-28 * --	1,13	
D,A	GB - A - 2 125 398 (SANDOZ) * Claims 13,14,95,96 * --	1,13	
A	US - A -3 405 134 (JUDD) * Column 1, lines 10-50 * --	1,10, 11,13	
P,A	EP - A2/A3 - 0 158 532 (A.H. ROBINS) * Abstract; page 6, lines 21-33 * --	1,10-13	TECHNICAL FIELDS SEARCHED (Int Cl 4)
A	CHEMICAL ABSTRACTS, vol. 82, no. 3, January 20, 1975, Columbus, Ohio, USA A.I. ERMAKOV "Use of mass spectrometry in structural and stereochemical studies. VI. Mass spectra of ß-oxoquinuclidines and their analogs" page 416, column 2, abstract no. 15805h & Khim. Geterosikl. Soedin. 1974, (7), 970-6 ----	1,11	

EPO Form 1503.3 06.78